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June 19, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm 1061
Rockville, MD 20852

Subject: Response to International Conference on Harmonization; Draft Revised Guidance on Q1A(R) Stability Testing of New Drug Substances and Products. Federal Register, Friday April 21, 2000, Docket # 93D-0139

To whom it may concern:

Novartis Pharmaceuticals Corporation has reviewed the above cited guidance and has the following comments:

Drug Substance:

1. "If it is suspected that failures may occur at accelerated conditions, it is recommended that additional test points be included".

We are under the impression that once failures occur at accelerated conditions then the studies should revert over to the intermediate test station (30°C/60%RH).

2. Why is the concept of "Significant Change" defined differently for Drug Substance and Drug Product?
3. Will it be possible to introduce additional testing into a stability program once a significant change has been observed without conducting additional stability studies? Would you please elaborate on a proposed process.
4. Please clarify: "If significant change occurs within the first 3 months testing at the accelerated storage condition, data should be supplied to cover the use of drug substance outside of the label storage condition".

Drug Product:

1. It is our opinion that release specifications are for internal usage and that shelf life specifications are considered "regulatory". In some cases they will differ and some cases not.

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2. Please see #4 under drug substance.
3. The term variability should be defined within the context of stability. It appears that this draft is equating the term variability with overall instability. Material can be unstable and yet stability studies will prove that there is very little variability from study to study and that is the data is consistent.

Additional Comments:

From the Glossary of Terms

Retest Period:

In the glossary section, the last sentence under "Retest Period" reads: "After this period, a batch destined for use in the manufacture of a drug product should be retested for compliance with specifications and then used immediately." This wording implies that extension of the retest period is not allowed, so that in effect the retest period becomes an expiry period. In the past FDA has allowed the practice of extending a retest period for a defined length of time and in development this is standard practice. Also, the term "used immediately" is open to interpretation. In the case of low volume products, "immediately" could be an indefinite period.

Formal Stability Studies:

As all studies are "formal", we suggest a more concise term, such as "primary" stability studies. This term is also consistent with FDA jargon.

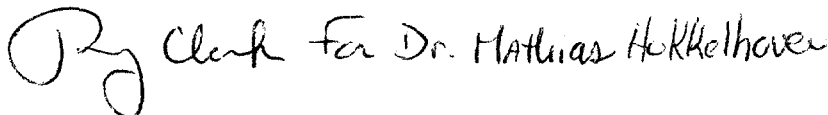
Other terminology used within the draft guidance:

Drug Product Packaging/Containers:

Clarify that the statement "*packaging proposed for marketing*" is the immediate container/closure system only. Stability studies of labeled, cartooned, shrink-wrapped packages (ie; secondary packaging) are not normally conducted.

Thank you for the opportunity to comment. If you have any questions, please contact me at (973) 781-6035.

Sincerely,

 Clerk for Dr. Mathias Hukkelhoven

Dr. Mathias Hukkelhoven
Vice President, Head US DRA
US Drug Regulatory Affairs

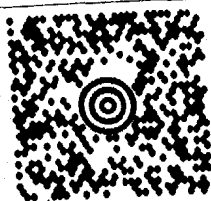
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